## REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.121, accompanying this amendment is Appendix A listing each of the above amendments to the application and identifying with particularity the changes that have been made.

Trauma leads to impairments in immunity by initiating an inflammatory response that predisposes the host to infectious complications. For injured patients who develop infectious sequelae, the consequences are often fatal. In the United States, more than 500,000 patients develop sepsis per year and only 55 to 65% survive.

It is well documented that even after stabilizing patients after serious injury, such as those incurred by motor vehicle accidents, burns, or life threatening blood loss from penetrating injury, those who survive for greater than 24 hours are most likely to die from infections that occur late following injury. In fact, of patients who survive the first 24 hours after serious injury, greater than 75% die as a result of late infectious complications such as pneumonia, generalized sepsis, or multiple organ dysfunction; all processes related to a compromised immune system.

Although numerous studies have demonstrated that injury induces a state of immunosuppression, the precise mechanisms are still under investigation. Prostaglandins have been associated with immune-compromised states and increased levels have been detected in inflammatory conditions, burns, and other injuries. Prostaglandin $E_2$ ($PGE_2$), in particular, is a major product of stimulated macrophages and is significantly elevated in immunocompromised states in human and animal models. It is one of the early mediators released after injury and is therefore a target for modulation of the immune response.

Prostaglandins are produced from free arachidonic acid by the enzyme cyclooxygenase (COX). Since the first description of prostaglandin synthesis inhibition by aspirin-like drugs, studies have evaluated the effects of blocking prostaglandin production. However, until recently, the use of non-steroidal anti-inflammatory drugs (NSAIDS) in the critically ill patient has been limited by gastrointestinal and other side effects. In 1991, a new isoform of COX was discovered, cyclooxygenase-2 (COX-2), that is expressed in sites of inflammation and injury and produced predominantly by macrophages. With the advent of selective COX-2 inhibitors, such as NS-398 (N-(2-cyclohexyloxy-4-nitrophenyl) methane sulfonamide), it has been possible to block the stress-induced production of prostaglandins and to better evaluate their role in the immune response to injury.

It has been previously demonstrated that after femur fracture and hemorrhage, mice demonstrate a maximal immune dysregulation at seven days after injury. This dysregulation has been correlated with decreased survival to a septic challenge. Specifically, mice are immunologically weaker and less able to recover when given an infectious challenge in the form of bacterial peritonitis, i.e. cecal ligation and puncture, or via fungal infection with the pathogen *Candida albicans*, after traumatic injury. In accordance with the present invention, it has been discovered that there is an increase in circulating prostaglandins early after such injuries as hemorrhage and fracture, and that administering a COX-2 inhibitor during the first 24 hours post-injury blocks this surge in circulating prostaglandins and markedly improves survival. It has also been discovered in accordance with the present invention that after trauma or injury, the prostaglandin receptors EP2 and EP4 are down regulated and that reversing this down regulation of receptor subtypes markedly improves survival.

The present invention provides methods of treating patients who have undergone shock, trauma, or other injury (including surgical insult) and who are at risk for developing infectious complications such as systemic inflammatory response syndrome. In one embodiment, the method comprises administering to a patient an effective amount of a selective inhibitor of cyclooxygenase-2 . In another embodiment, the method comprises administering an effective amount of a drug which either stimulates one or more $PGE_2$ receptors (e.g., EP1, EP2, EP3, or EP4 receptor subtypes) or interferes with binding of $PGE_2$ to one or more of the $PGE_2$ receptor subtypes. The present invention, therefore, provides therapeutic intervention which selectively modulates the immune response after trauma, reduces the incidence of infectious complications, and improves survival after traumatic injury.

The rejection of claims 1-2, 9, 12, and 15 under 35 U.S.C. § 103 for obviousness over Shoup, et. al., "Cyclooxygenase-2 Inhibitor NS-398 Improves Survival and Restores Leukocyte Counts in Burn Infection," J. Trauma 45(2): 215-20 (1998)("Shoup"), U.S. Patent No. 5,633,272 to Talley et. al. ("Talley"), or WO 99/30721 to Dannenberg et. al. ("Dannenberg") is respectfully traversed.

Shoup tests the *in vivo* efficacy of the COX-2 inhibitor NS-398 by subjecting mice to a 15% dorsal scald burn plus 1000 colony-forming units of topical *Pseudomonas aeruginosa* and then administering the COX-2 inhibitor. Subjecting the mice to both burn and infection at the same time is a multiple trauma injury which is different than just a burn injury. There is no way of knowing whether the infection or the burn caused the

inflammatory response. As a result, any beneficial results achieved with NS-398 cannot be correlated to its effect on burn injury as opposed to infection.

Talley is directed to a class of substituted isoxazolyl compounds for use in treating inflammation and inflammation-related disorder specific diseases, including pain and headaches, fever, arthritis, asthma, bronchitis, menstrual cramps, tendonitis, bursitis, skin-related conditions, gastronintestinal conditions, vascular diseases, migraine headaches, periarteritis nodosa, thyroiditis, aplastic anemia, Hodgkin's Disease, scleroderoma, rheumatic fever, type I diabetes, myasthenia gravis, sarcoidosis, nephritic syndrome, Behcet's syndrome, polymyositis, gingivitis, hypersensitivity, conjunctivitis, swelling occurring after injury, and myocardial ischemia.

Dannenberg uses selective COX-2 inhibitors to treat liver disease, including inflammatory liver disease. The selective COX-2 inhibitors are said to have improved efficacy over other COX-2 inhibitors in the treatment of inflammatory conditions, including arthritis, inflammatory bowel disease, diabetes, Alzheimer's Disease, pancreatitis, inflammatory vascular and ocular disorders, and liver disease. Cancer may also be treated with such inhibitors.

Neither Shoup, Talley, nor Dannenberg suggest using a selective COX-2 inhibitor in a method for prophylaxis or treatment of a patient at risk for systemic inflammatory response syndrome and complications wherein the patient at risk for systemic inflammatory response syndrome and complications thereof is a patient who has sustained at least one of trauma, burn injury, life threatening blood loss from penetrating injury, or a patient who has undergone surgery. Although these references teach using such inhibitors to treat pain, chronic disease, or the combination of burn and infection, no where do they suggest that COX-2 inhibitors are useful in preventing or treating the claimed conditions. Moreover, the ability of such inhibitors to treat pain, chronic disease, or the combination of burn and infection, would not lead those skilled in the art to believe that administration of COX-2 inhibitors could be used to treat a patient at risk for systemic inflammatory response syndrome and complications thereof where the patient has sustained at least one of trauma, burn injury, life threatening blood loss from penetrating injury, or a patient who has undergone surgery. The discovery by applicants that this is possible with COX-2 inhibitors is a significant and unobvious advance beyond the state of the art reflected by Shoup, Talley, and Dannenberg. Accordingly, the rejection over these references should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowanced is earnestly solicited.

Respectfully submitted,

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Date 3/7/03 | Cheryl S. Mascitti

**Appendix A**
**Version With Markings to Show Changes Made**


In reference to the amendments made herein to claim 1, additions appear as underlined text, while deletions appear as bracketed text, as indicated below:

In the Claims:

1. (Amended) A method of prophylaxis of a patient at risk for systemic inflammatory response syndrome and complications thereof or of treating a patient having systemic inflammatory response syndrome or complications thereof, which comprises administering to said patient a therapeutically effective amount of a selective inhibitor of cyclooxygenase-2, wherein the patient at risk for systemic inflammatory response syndrome and complications thereof is a patient who has sustained at least one of trauma, burn injury, life threatening blood loss from penetrating injury, or a patient who has undergone surgery.